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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/853,731	05/11/2001	Apollon Papadimitriou	20619	6504

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HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110

KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,731	PAPADIMITRIOU, APOLLON	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29,31,32,34-47,49,50 and 52-66* is/are rejected.

7)☒ Claim(s) *30,33,48 and 51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of a modified sequence of human erythropoietin (EPO), $Asn^{30}Thr^{32}Val^{87}Asn^{88}Thr^{90}$ in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In the response to restriction requirement, applicants indicate the election of a specific modified sequence of human EPO is a species election, however, the office action dated September 27, 2002 (paragraph 1) and the telephone conversation with applicant on October 7, 2002 indicate the election of one modified sequence is not a species election, rather an election of patentably distinct invention because each peptide with a specific sequence is considered patentably distinct.

Notice

2. Claim 20, for example, contains "$[poly(ethylene\ glycol)]_n$". Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. Applicant has used "$[poly(ethylene\ glycol)]_n$" in such a manner that appears that the instant brackets would indicate material that needs to be printed but would be indistinguishable from deleted material and is thus, confusing as to whether the glycoprotein in claim 20 would be covalently linked to "$(poly(ethylene\ glycol))_n$" or not. The applicant can only amend by cancellation and presentation of a new claim. See also changes to 37 CFR 1.121 in Amendment rules package (Final Rule published on 8 Sep. 2000 (65 Fed. Reg. 54603), see also O. G. of 19 Sep. 2000 (1238 Off. Gaz. Pat. Office 77)). Please see also claims 21, 23-25, 45, 46 and 48-50.

Claim Objections

3. Claims 15, 18, 40 and 43 are objected to because the claims contain non-elected sequence modifications.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1, 19-21, 26 and 44-47 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 10/041,363.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 19-21, 26 and 44-47 in the instant application disclose a pharmaceutical composition comprising an EPO glycoprotein product having the in vivo biological activity, wherein the glycoprotein product is a pegylated EPO such as EPO being linked to $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$. This is an obvious variation in view of claims 1-16 in the copending application which disclose a conjugate comprising an EPO glycoprotein having N-terminal α-amino group and one poly(ethyleneglycol), where EPO is linked to $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$, and a pharmaceutical composition comprising the conjugate. Thus, both the

instant application and the copending application are directed to a pharmaceutical composition comprising a conjugate of EPO with poly(ethyleneglycol). Claims 1, 19-21, 26 and 44-47 in present application and claims 1-16 in the copending application are obvious variations of a pharmaceutical composition comprising a conjugate of EPO with poly(ethyleneglycol) having the in vivo biological activity.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-25, 39-43, 45-47, 49, 50, 52-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1-21, 23-25 and 62-66 are indefinite because of the use of the term "a portion of said solution". The term "a portion of said solution" renders the claim indefinite, it is unclear what amount of solution is administered as to "a portion of said solution" and would appear to be extraneous recitation. Claims 2-21, 23-25 and 63-66 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

7. Claims 20, 21 and 45-47 are indefinite because of the use of the term "a linker of the formula $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$". The term "a linker of the formula $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$" renders the claim indefinite, it is unclear how the glycoprotein is covalently

linked to poly(ethylene glycol) by a linker which already contains the formula of poly(ethylene glycol). Claim 20 has no antecedent basis for "the sequence of human erythropoietin" in claim 19 nor in claim 1. Claims 21 and 46-47 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

8. Claim 12 would appear (by claim dependency) to require EPO to be a transcriptional/translational activator of itself- note "..the product is expressed by endogenous gene activation". It is unclear in claim 12 or claim 1 how this is accomplished by the claimed composition.

9. Claim 15 and 40 for clarity should indicate a reference sequence to which the recited residue positions refer, see also claims 17, 18, 42 and 43.

10. Claims 39 and 41 have no antecedent basis for "the sequence of human erythropoietin" in claim 26.

11. Claim 22 (not amended) is indefinite because the claim depends from a claim with a higher claim number (claim 36). Claim 22 also recites the limitation "formula (I)" in line 1. There is insufficient antecedent basis for this limitation in the claim.

12. Claims 21, 24, 25, 46, 47 and 49-50 are indefinite because of the use of the term "P is the residue of the erythropoietin glycoprotein without the n amino group(s)". The term "P is the residue of the erythropoietin glycoprotein without the n amino group(s)" renders the claim indefinite, it is unclear whether P is the EPO glycoprotein without the n amino group, or the residue of the EPO glycoprotein without the n amino group since the claim indicates the formula is the pegylated EPO product. Claims 47 is included in the rejection because they are dependent

on a rejected claim and do not correct the deficiency of the claim from which they depend. Claims 25 and 50 are unclear as to the recitation of "whewrein".

13. Claim 52, for example, recites the limitation "methionine" in line 1 and "polyol" in line 2. There is insufficient antecedent basis for this limitation in the claim. See also claims 53-61 for reciting " mannitol", "methionine", "NaCl", "arginine", "pluronic F68" in the claim. Claim 52 is also indefinite because of the use of the term "20 mM per liter", it is not clear what the term "20 mM per liter" means since "mM" is the concentration per unit volume, e.g. mmoles per liter.

14. Claim 66 is indefinite because of the use of the term "towater" or "ml. of said solution". The term "towater" or "ml. of said solution" renders the claim indefinite, it is unclear what the term means as to "towater", and whether the claim includes the limitation "of said solution" because the claim ends with the first period "."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-4, 6, 7, 9-12, 26-29, 31, 32, 34-37, 54 and 62-64 are rejected under 35 U.S.C. 102(b) as anticipated by Woog *et al.* (U. S. Patent 4,992,419).

Woog *et al.* disclose a compatible, storage-stable, aqueous or lyophilized EPO preparation containing human protein, phosphate or citrate buffer (20-100 mM), isotonic agent such as NaCl or mannitol at pH 6.5-7.4, and an amino acid such as arginine, and the preparation ensures the in-vivo effectiveness of the protein (column 1, lines 5-10; column 2, line 28-column

3, line 23; claims 1-4, 6, 7, 9-12; 62-64). One preparation (Table 1, compositions a) contains 1000 U/ml of EPO, which corresponds to 10 or 5 μg/ml (the EPO preparation has an activity of 100,000 to 200,000 units/mg protein, corresponding to 100 to 200 units/μg; column 3, lines 25-30), 4 mg/ml NaCl (68 mM), 0.55 mg/ml of NaH_2PO_4 (5.3 mM), 5.0 mg/ml of Na_2HPO_4 (40 mM; claims 2-29, 31, 32, 34-37 and 54).

16. Claims 1-9, 11, 12, 62-64 and 66 are rejected under 35 U.S.C. 102(b) as anticipated by Zale *et al.* (WO 96/40073).

Zale *et al.* disclose a solution mixture, which is used for preparing a composition of sustained release of non-aggregated EPO formulation, contains a biologically active EPO, anti-aggregation agent such as NaCl, Na_2SO_4 or mannitol, a phosphate or citrate buffer (5 mM), at pH 5.0-7.0 (page 4, lines 13-19; page 5, line 33-page 6, line 22; page 6, line 28-page 7, line 15; page 14, lines 7-14; claims 1-9, 11 and 12). The stock EPO solution contains 1 mg/ml of EPO, which is dialyzed against formulation buffer such as a phosphate or citrate buffer (5 mM), and the formulation can be lyophilized to powder (claim 62-64) and contains 10% EPO solution which is about 100 μg/ml of EPO (Example 1 and Table 1; claim 66).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-4, 6, 7, 9-13, 26-29, 31, 32, 34-38, 54 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woog *et al.* (U. S. Patent 4,992,419) in view of Rosen *et al.* (WO 92/06116).

Woog *et al.* disclose compatible, stable-stable, aqueous or lyophilized EPO preparations containing human protein, phosphate or citrate buffer (20-100 mM), isotonic agent such as NaCl or mannitol at pH 6.5-7.4, and an amino acid such as arginine, and the preparation ensures the in-vivo effectiveness of the protein (column 1, lines 5-10; column 2, line 28-column 3, line 23; claims 1-4, 6, 7, 9-12; 62-64). One preparation (Table 1, compositions a) contains 1000 U/ml of EPO, which corresponds about 10 or 5 μg/ml (the EPO preparation has an activity of 100,000 to 200,000 units/mg protein, corresponding to 100 to 200 units/μg; column 3, lines 25-30), 4 mg/ml NaCl (68 mM), 0.55 mg/ml of NaH_2PO_4 (5.3 mM), 5.0 mg/ml of Na_2HPO_4 (40 mM; claims 2-29, 31, 32, 34, 35-37 and 54). However, Woog *et al.* do not disclose the amino acid sequence of human EPO. Rosen *et al.* teach the amino acid sequence of recombinant human EPO (page 7, lines 32-34; SEQ ID NO:3 of WO 92/06116). At the time of invention was made, it would have been obvious to one of ordinary skill in the art to use the recombinant human EPO taught by Rosen *et al.* to prepare the pharmaceutical composition as taught by Woog *et al.* (claims 13 and 38) because one of ordinary skill in the art would have been motivated to use the recombinant human EPO for preparing the pharmaceutical composition because the use of recombinant protein would avoid the possibility of contamination from tissue. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

18. Claims 1-4, 6, 7, 9-12, 14-17, 26-29, 31, 32, 34-37, 39-42, 54 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woog *et al.* (U. S. Patent 4,992,419) in view of Elliot *et al.* (EP 0640619).

Woog *et al.* disclose compatible, stable-stable, aqueous or lyophilized EPO preparations containing human protein, phosphate or citrate buffer (20-100 mM), isotonic agent such as NaCl or mannitol at pH 6.5-7.4, and an amino acid such as arginine, and the preparation ensures the in-vivo effectiveness of the protein (column 1, lines 5-10; column 2, line 28-column 3, line 23; claims 1-4, 6, 7, 9-12; 62-64). One preparation (Table 1, compositions a) contains 1000 U/ml of EPO, which corresponds about 10 or 5 μg/ml (the EPO preparation has an activity of 100,000 to 200,000 units/mg protein, corresponding to 100 to 200 units/μg; column 3, lines 25-30), 4 mg/ml NaCl (68 mM), 0.55 mg/ml of NaH_2PO_4 (5.3 mM), 5.0 mg/ml of Na_2HPO_4 (40 mM; claims 2-29, 31, 32, 34, 35-37 and 54). However, Woog *et al.* do not disclose the use of a modified human EPO in the composition. Elliot *et al.* teach EPO analogs having at least one additional site for glycosylation or a rearrangement of at least one site for glycosylation, such as the modified EPO with $Asn^{30}Thr^{32}Val^{87}Asn^{88}Thr^{90}$ (page 3, lines 21-28; page 19, Table 3, line 22). At the time of invention was made, it would have been obvious to one of ordinary skill in the art to use the modifed human EPO taught by Elliot *et al.* to prepare the pharmaceutical composition as taught by Woog *et al.* (claims 14-17 and 39-42) because one of ordinary skill in the art would have been motivated to use the modified EPO for preparing the pharmaceutical composition because the modified EPO having additional glycosylation site would have better in vivo activity due to its higher sialic acid content in the glycosylated protein. Thus, the combined references

result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

19. Claims 30, 33, 48 and 51 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

20. Claims 1-29, 31, 32, 34-47, 49, 50, 52-66 are rejected, and claims 30, 33, 48 and 51 are objected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D.
Patent Examiner

Christopher S. F. Low

CHRISTOPHER S F LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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January 7, 2003